Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma).

Bibliographic Source(s)

Dearden C, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, McMillan A. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). London (UK): British Committee for Standards in Haematology (BCSH); 2013 Aug. 99 p. [359 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Dearden C, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, McMillan A, British Committee for Standards in Haematology. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). Br J Haematol. 2011 May;153(4):451–485.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Diagnosis and Staging

- Diagnosis requires expert examination of tissue including a detailed phenotypic assessment. Clonality should be assessed by polymerase chain reaction (PCR) for T-cell receptor (TCR) gene rearrangements. This is the subject of a separate British Committee for Standards in Haematology (BCSH) guideline.
- Staging should include blood and bone marrow examination and radiology as well as assessment of performance status and prognostic factors to allow assignment of a prognostic score and planning of therapy.
- Lumbar puncture/magnetic resonance imaging (MRI) of brain is not routinely required in the absence of central nervous system (CNS) symptoms or signs.
- Positron emissions tomography (PET) scanning is not established in the routine staging of peripheral T-cell lymphoma (PTCL).
- The T-cell malignancies are rare and often complex diseases. Diagnosis and management should be discussed in a network multi-disciplinary team meeting and those patients requiring treatment should generally be referred to a cancer centre or tertiary centre with specialist expertise.

Prognosis

- The International Prognostic Index (IPI) gives useful prognostic information in PTCL and should be calculated, but it clusters many cases in the higher risk groups.
- Newer T-cell specific prognostic scores appear to be more discriminatory and may be valuable in prospective trials.

Mature T-cell Leukaemias

T-prolymphocytic Leukaemia (T-PLL)

- Intravenous alemtuzumab should be used as first line therapy for T-PLL (Grade 1B).
- Patients failing to respond should receive the combination of alemtuzumab plus pentostatin or another purine analogue (Grade 1C).
- All eligible patients should proceed to either autologous or allogeneic stem cell transplant in first remission (Grade 1C).
- Patients should be entered into clinical trials wherever possible.

T-large Granular Lymphocytic Leukaemia (T-LGL)

- Patients do not require therapy unless symptomatic from cytopenias or other complications.
- The majority of cases will follow an indolent course and aggressive chemotherapy is not indicated.
- The decision to treat is based on: significant symptomatic anaemia (<9 g/dl) and/or the need for transfusion; severe neutropenia (<0.5 $x10^9$/l) associated with infection; severe thrombocytopenia (<50 x 10^9/l); or any combination of these.
- Oral ciclosporin or weekly oral low dose methotrexate (10 mg/m^2/week) are effective in more than 75% of cases (Grade 1B).
- Responses may be enhanced by the use of growth factors (erythropoietin and/or granulocyte colony stimulating factor [G-CSF] (Grade 1B).
- Second line treatments include purine analogues (pentostatin), cyclophosphamide and alemtuzumab (Grade 1B).

Chronic Lymphoproliferative Disease of Natural Killer (NK) Cells (CLPD-NK)

Management same as for T-LGL.

Aggressive NK-cell Leukaemia

- Rare aggressive NK-cell leukaemias occurring in younger adults require a different therapeutic approach and consideration of stem cell transplantation (Grade 2C).
- Patients should be entered into clinical trials wherever possible.

Adult T-cell Leukaemia Lymphoma (ATL)

- Exclude co-infection with strongyloides prior to commencing therapy.
- Appropriate antimicrobial prophylaxis during therapy should be instituted for seropositive patients.
- Smouldering and chronic:
  - No benefit from early chemotherapy therefore watch and wait
  - Zidovudine (ZDV) + Interferon (IFN)α +/- monoclonal antibodies (MoAbs) may be considered (especially in chronic ATL) in the context of a clinical trial (Grade 1B).
- Lymphoma type:
  - Induction with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or alternative multi-agent regimen plus G-CSF (Grade 1B) with concurrent ZDV + IFNα (Grade 1B)
  - ZDV + IFNα maintenance +/- MoAbs *OR* Allogeneic transplant in 1st complete remission (CR) for eligible patients (Grade 2C)
- Leukaemia (acute) type:
  - Induction with anti-retroviral therapy alone (ZDV + IFNα) *OR*
  - Induction with CHOP or alternative multi-agent regimen plus G-CSF (Grade 1B) + concurrent ZDV + IFNα
  - Allogeneic haemopoietic stem cell transplantation (allo-HSCT) in 1st CR for eligible patients (Grade 1B) *OR*
  - ZDV + IFNα maintenance +/- MoAbs (Grade 2C) *OR*
  - Consolidation with novel agents (e.g., arsenic trioxide, IFNα); proteasome inhibitor in clinical trials
- CNS prophylaxis should be considered using the same criteria as for diffuse large B-cell non-Hodgkin lymphoma (NHL) (Grade 2C).

Nodal PTCL

PTCL, Not Otherwise Specified (PTCL-NOS)

- Primary treatment of PTCL-NOS should be within the context of a clinical trial if possible as standard therapy gives disappointing results (Grade 1B).
- Outside trial, CHOP remains the standard therapy. Consideration should be given to consolidation with autologous haemopoietic stem cell transplantation (auto-HSCT) (Grade 2B).
- Relapsed or refractory disease should be treated with relapse-schedule combination chemotherapy and considered for allo-HSCT with reduced intensity conditioning (Grade 2B) or autologous stem cell transplantation (Grade 2B) or novel therapies within a trial setting.
- Outside a trial a number of agents show promise, particularly gemcitabine, bendamustine, pralatrexate and romidepsin but the data are insufficient to recommend routine use.
- CNS prophylaxis should be considered using the same criteria as for diffuse large B-cell NHL (Grade 2C).

Angio-immunoblastic T-cell Lymphoma (AITL)

- The timing and selection of therapy depend on clinical presentation and prognostic features.
- Patients requiring therapy should be entered into available clinical trials where possible.
- Outside a clinical trial, CHOP or fludarabine + cyclophosphamide (FC) would be considered as standard therapies (Grade 1B).
- Immunomodulatory therapies such as steroids, ciclosporin, thalidomide and lenalidomide have some evidence of efficacy in chemo-refractory cases (Grade 2B).
- Consolidation with auto-HSCT should be considered for patients with chemosensitive disease in first remission or after relapse (Grade 2B).
- Routine CNS prophylaxis is not warranted.

Anaplastic Large Cell Lymphoma (ALCL)

- The IPI has predictive value in ALCL but anaplastic lymphoma kinase (ALK) positivity is the most important prognostic factor.
- Patients with limited stage anaplastic large cell lymphoma and no adverse prognostic features by IPI should be treated with 3 to 4 cycles of CHOP chemotherapy and involved field radiotherapy.
- All other patients should be entered into a clinical trial or receive 6 to 8 cycles of CHOP chemotherapy (Grade 1A).
- ALK-neg ALCL should be treated as for PTCL-NOS.
- Primary cutaneous ALCL (ALK-neg) should be managed with local excision +/- radiotherapy and chemotherapy reserved for those patients with systemic disease.
- At relapse patients should receive platinum-based chemotherapy or an alternative salvage regimen such as brentuximab vedotin and patients with chemosensitive disease should be considered for transplant.

Extranodal PTCL

Extranodal NK/T-cell Lymphoma, Nasal Type

- Diagnosis and staging uses the same investigations and techniques as for PTCL-NOS. Demonstration of Epstein-Barr virus (EBV) in the biopsy is important diagnostically.
- Assigning a conventional IPI score is of limited value as most cases are localised and have a low score, yet the survival is still poor (Grade 1B).
- The distinction at diagnosis between localised disease and disseminated disease is important as the latter has a dismal prognosis and might be considered for experimental therapy as first line if available (Grade 1B).
- Assessment of EBV by PCR can be helpful in monitoring disease and may have prognostic relevance.
- Outcome is unsatisfactory with CHOP-like therapy and entering patients into relevant clinical trials if available is recommended.
- Patients with localised disease should receive radiation with 50–55 Gy (Grade 1B).
- The value of additional chemotherapy (CHOP, etoposide-based or asparaginase-based) for local disease remains unclear but is considered conventional pending more information (Grade 1B).
- Asparaginase-containing regimens should be considered in disseminated first-line and in relapsed or refractory disease (Grade 1B).
- High dose therapy is unproven and there is no basis to recommend it outside a trial.

Enteropathy-associated T-cell Lymphoma (EATL)

- Diagnosis and staging use the same investigations and techniques as for PTCL-NOS. In addition, it is important to liaise with an experienced gastroenterologist to assist with biopsy, staging and follow up and to manage nutritional problems (Grade 1C).
- Assigning a conventional IPI score is of limited value as there is no good prognostic group and most cases are stage I-IIE.
- If there are trials available at the time of diagnosis, entry should be strongly considered as there is no satisfactory standard therapy.

- CHOP-like therapy, with or without an up-front autograft remains a common approach outside a trial and adoption of a more intensive approach such as the National Cancer Research Institute/Scottish and Newcastle Lymphoma Group (NCRI/SNLG) protocol is a reasonable option in fitter patients (Grade 2B).
- Nutrition is a major issue in managing these patients and dietetic/gastroenterology advice is essential at all stages of treatment and follow-up (Grade 1C).

Hepatosplenic T-cell Lymphoma

- No satisfactory recommendations can be made from the limited evidence base.
- Trial or experimental therapy should be considered if available.
- Allogeneic bone marrow transplantation could be considered but the evidence is purely anecdotal.
- Conventional chemotherapy approaches as for PTCL-NOS are the default and there are some survivors reported in the literature (Grade 2C).

Subcutaneous Panniculitis-like T-cell Lymphoma (SPTCL)

- No conclusive recommendations can be made from the limited evidence base. The cases described in the literature are not uniform.
- This is not a universally aggressive disease and careful initial assessment and observation should be undertaken before committing to treatment (Grade 2C).
- CHOP-like chemotherapy appears to be effective and produces survivors (Grade 2C).
- Relapsed disease may respond to dose intensification in some patients (Grade 2C).
- Local radiotherapy has a place for good prognosis localised symptomatic skin involvement which does not resolve with topical steroids (Grade 2C).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Mature T-cell and natural killer (NK)-cell neoplasms (excluding cutaneous T-cell lymphoma)

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Dermatology

Hematology

Internal Medicine

Medical Genetics

Oncology

Pathology

Radiation Oncology

Radiology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals with clear guidance on the management of patients with mature T-cell and natural killer (NK)-cell neoplasms

Target Population

Patients with mature T-cell and natural killer (NK)-cell neoplasms (excluding cutaneous T-cell lymphoma)

Note: The guidance may not be appropriate to all patients in this disease group.

Interventions and Practices Considered

Diagnosis/Evaluation

1. Expert examination of tissue including a detailed phenotypic assessment
2. Blood and bone marrow examination
3. Radiology
4. Assessment of performance status and prognostic factors using the International Prognostic Index (IPI) or other scoring system
5. Lumbar puncture (not routinely recommended)
6. Magnetic resonance imaging (MRI) (not routinely recommended)
7. Positron emission tomography (not routinely recommended)
8. Demonstration of Epstein-Barr virus (EBV)

Prevention

1. Antimicrobial prophylaxis
2. Central nervous system (CNS) prophylaxis

Treatment

1. Intravenous alemtuzumab
2. Purine analogue (pentostatin)
3. Autologous or allogeneic stem cell transplantation
4. Oral ciclosporin
5. Oral low-dose methotrexate
6. Growth factors (erythropoietin, granulocyte colony stimulating factor [G-CSF])
7. Cyclophosphamide
8. Anti-retroviral therapy (zidovudine, interferon-α, monoclonal antibodies)
9. Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other multi-agent regimen + G-CSF
10. Novel agents (e.g., arsenic trioxide)
11. Fludarabine + cyclophosphamide (FC)
12. Entry of patients into clinical trials when possible
13. Immunomodulatory therapy (steroids, ciclosporin, thalidomide, lenalidomide)
14. Radiotherapy
15. Local excision
16. Salvage therapy with brentuximab vedotin
17. Etoposide- or asparaginase-based chemotherapy
18. Autograft
19. Nutrition considerations

Note: There are insufficient data to recommend novel agents such as gemcitabine, bendamustine, pralatrexate, and romidepsin.

Major Outcomes Considered

- Effectiveness of diagnosis and staging, according to clinical, haematologic, cytogenetic, pathologic and imaging features of disease
- Predictive value of prognostic tests
- Efficacy and effectiveness of treatments (e.g., measured by response rate, duration of response, remission rate, disease progression and survival)
- Treatment-related toxicity

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of the guidelines involved review of key literature in English, including MedLine, EMBASE and Internet searches up to December 2012.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Assessment of the level of evidence was based on the literature review and a consensus of expert opinion. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been used to quote the levels of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This guideline is an update of the 2010 guideline compiled by a T-cell Working Group on behalf of the British Committee for Standards in Haematology (BCSH). The guideline group was selected to be representative of UK-based medical experts and patient representatives and

included 5 UK haematologists, 2 with a background in stem cell transplantation, 1 medical oncologist and a dermatologist. Advice was also sought from experts in radiation oncology and patient advisory groups.

The production of the guidelines involved the following steps:

- Consultation with representatives of other specialities including clinical oncology.
- Assessment of the grade of recommendation was based on the literature review and a consensus of expert opinion. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been used to quote the grades of evidence (see the "Rating Scheme for the Strength of the Recommendations" field).
- Adherence to the BCSH procedure for guidelines development (http://www.bcshguidelines.com/40_BCSH_PROCESS.html).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of mature T-cell and natural killer (NK)-cell neoplasms (excluding cutaneous T-cell lymphoma)

Potential Harms

Treatment-related toxicity and side-effects

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society of Haematology nor the publishers accept any legal responsibility for the content of these guidelines.
- The guidance may not be appropriate to all patients in this disease group and in all cases individual patient circumstances may dictate an alternative approach.
- It should be recognised that limited evidence was available and that no grade A recommendations could be made because of lack of data from randomised controlled trials.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Dearden C, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, McMillan A. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). London (UK): British Committee for Standards in Haematology (BCSH); 2013 Aug. 99 p. [359 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 May (revised 2013 Aug)

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology Writing Group

Composition of Group That Authored the Guideline

Writing Group Members: C Dearden, The Royal Marsden NHS Foundation Trust, London; R Johnson, St James Hospital, Leeds; R Pettengell, St George's Hospital, London; S Devereux, Kings College Hospital, London; K Cwynarski, Royal Free Hospital, London; S Whittaker, St Johns Institute of Dermatology, London; A McMillan, Nottingham University Hospital NHS Trust, Nottingham

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Dearden C, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, McMillan A, British Committee for Standards in Haematology. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). Br J Haematol. 2011 May;153(4):451–485.

Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 18, 2013.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion-criteria.aspx.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.